CLINICAL VIGNETTE

An Adult with Severe Phenotype of Roifman Syndrome

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Case Presentation

A 36-year-old female was admitted for acute kidney injury (AKI). She has complex past medical history of Roifman syndrome, cirrhosis, chronic kidney disease, Type II diabetes mellitus, hypothyroidism, pancytopenia, and severe malnutrition. She is a custodial resident at a skilled nursing facility. She is nonverbal at baseline, but understands basic concepts like "food" and "pain" and turns in response to her name.

Previous genetic testing confirmed that she is homozygous for *RNU4ATAC c.16G>A*, pathogenic variants associated with Roifman syndrome. Family history is limited though she has several siblings who are not diagnosed with Roifman syndrome and are otherwise healthy.

On admission, her exam was notable for a BMI of 10.6 kg/m^2 (height 121.9cm and weight 15.7kg). She appeared severely malnourished and cachectic with marked scoliosis and no muscle tone or bulk present in the upper or lower extremities. She had microcephaly, a long philtrum, and thin upper lip, consistent with Roifman syndrome. She also had talipes cavus bilaterally, brachydactyly of the hands and feet, and clinodactyly of the 5th digit of her hands bilaterally.

Complete blood count (CBC) was notable for hemoglobin 8.7g/dL, white blood cell (WBC) count 3.29k/uL, and platelet count 68k/uL. Complete metabolic panel (CMP) included potassium 6.4mmol/L, Creatinine 2.01mg/dL (baseline 1.3-1.5mg/dL), AST 92U/L, and ALT 43U/L. Urinalysis revealed pH of 7.5, negative ketones, negative protein, negative nitrite, 3+ leukocyte esterase, >200 WBC per HPF, and WBC clumps. Subsequent urine culture grew 50,000 CFU/mL of Proteus Mirabilis, consistent with chronic colonization. Given her recurrent AKIs, she underwent an evaluation for anatomic abnormalities that could explain her presentation. Bilateral renal ultrasound demonstrated markedly atrophic kidneys, 6.3cm on the left and 3.5cm on the right. On a prior admission, CT of the abdomen and pelvis revealed liver cirrhosis and splenomegaly, though synthetic function remained intact.

The patient received fluid resuscitation and was treated empirically with Fosfomycin 2g via g-tube due to concern for urinary tract infection prior to her urine culture resulting.

Discussion

Roifman syndrome is a rare autosomal recessive syndrome characterized by humoral immunodeficiency, spondyloepiphyseal dysplasia, retinal dystrophy, and developmental delay.[1] It belongs to a family of spliceosomopathies, including Lowry-Wood syndrome, caused by pathogenic variants in the RNU4ATAC gene on Chromosome 2.[2] While biallelic pathogenic variants of Roifman syndrome have been identified in several children, no cases to date document the phenotype into adulthood. Here, we discuss a young adult woman's severe phenotype with multi-organ involvement.

Nearly all individuals with documented Roifman syndrome have characteristic dysmorphic facial features, including microcephaly, long philtrum, and a thin upper lip.[3] While hypotonia, scoliosis, developmental delay, and postnatal growth deficiency are also well documented in Roifman syndrome and other RNU4ATAC-opathies. No case reported to date describes an individual with such severe malnutrition and muscle wasting as in this case. Moreover, the cognitive impairment noted in previous cases has been comparatively mild. Two young siblings with Roifman syndrome exhibited little to no intellectual delay, with the older able to participate in mainstream schooling.[4] There should be a low threshold to evaluate and monitor children with Roifman syndrome for developmental delays, particularly related to speech, language, and cognition.

Immunodeficiency, leukopenia, and recurrent infections are also universal components of Roifman syndrome. The pancytopenia noted in our case is the patient's chronic baseline. Her anemia is likely multifactorial, due to chronic disease, malnutrition, and chronic kidney disease. Her decade-long history of thrombocytopenia is likely due to defects in megakaryocyte differentiation, which is also consistent with other cases of Roifman syndrome. It is likely to worsen with cirrhosis and splenomegaly.[5] Transfusion thresholds currently are not different for patients with Roifman syndrome and other RNU4ATAC-opathies. Rather, protocols should encourage clear documentation of baseline blood counts for patients in order to minimize unnecessary admissions and healthcare costs associated with treating each abnormal lab value.

The etiology of this patient's liver cirrhosis remains an ongoing question, as no liver biopsy has been performed. Previously described gastrointestinal abnormalities associated with Roifman syndrome have been limited to neonatal cholestasis,

hepatosplenomegaly, and mild hepatic fibrosis.[4,6] Due to limitations in obtaining a precise chronological history, it is difficult to delineate whether the development of cirrhosis in this case is primarily due to anorexia, or her chronic severe malnutrition Additionally, autoimmune hepatitis has been found in some patients with Roifman syndrome, with several autoimmune conditions associated with Roifman syndrome likely stemming from dysfunction of T-cell immunity.[7]

Similar to the patient's liver disease, renal tubular dysfunction may occur in infanthood through late childhood in Roifman syndrome due to a range of mechanisms.[8] Multiple processes could explain the patient's renal atrophy, including recurrent infections and chronic kidney disease. In subsequent admissions, the patient's renal function has been assessed with Cystatin-C. This may be a more reliable marker of renal function in the setting of the metabolic and nutrition complications seen in patients with Roifman syndrome, particularly with low muscle mass.

The clinical presentation of patients with Roifman syndrome and other RNU4ATAC-opathies is heterogeneous. The severity of this adult patient's multi-system involvement may contribute to future diagnosis, treatment, and long-term care.

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